DRUG METABOLISM

& PHARMACOKINETICS („DMPK“)

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OFFERING

Over the past 20 years, Evotec has developed expertise in numerous therapeutic areas including diseases of the central nervous system (“CNS”), pain, oncology, diabetes and metabolic diseases, inflammation and anti-infectives.

This collective experience has consolidated the view that successful small molecule drug discovery requires a deep understanding of biological context coupled with knowledge and experience of the property space required to deliver safe, efficacious drugs. DMPK continues to be a key player in this success since the major sources of attrition – clinical efficacy and safety – are clearly linked to exposure in key tissues either on- or off-target.

We understand that each partner has different needs, internal capabilities and capacities and Evotec prides itself in being able to provide flexible, innovative and efficient solutions.

Evotec’s experienced scientists can support your aspirations in a variety of ways, providing mechanistic interpretation as well as timely delivery of quality data. We firmly believe that the co-location and interaction of disciplines (e.g. DMPK, synthetic and medicinal chemistry, computational science and structural biology) enhances the overall design, analysis and communication process: More learning cycles per unit time = more knowledge and experience = better quality output. More, better-informed decisions = less waste.

Collectively, this group of experienced scientists has made significant contributions to discovery projects throughout their careers:

- >90 development candidates
- Named inventors and authors on >750 patents and publications

Evotec offers a comprehensive and flexible range of *in vitro* and *in vivo* DMPK studies designed to cover the majority of activities in the screen-to-candidate phase. The scientific expertise and processes are accessed in a variety of ways by our partners and project teams.

IN VITRO COMPOUND SCREENING AND PROFILING

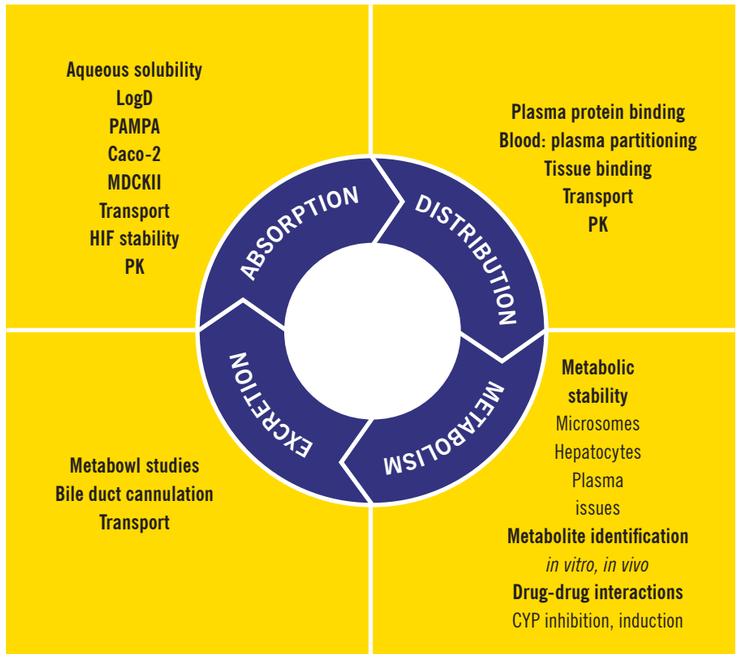
Routine compound testing (e.g. weekly cycle times)

Evotec’s combination of routine *in vitro* assays and our flexibility to address your individual requirements enables us to offer a truly bespoke, differentiated service: Experienced DMPK scientists delivering data of excellent quality coupled with validated, cost efficient and highly automated processes. Interpretation of data and consultation is provided by our DMPK experts within integrated project teams.

For integrated projects, a range of physico-chemical assays are available together with analysis of permeability (PAMPA, Caco-2, MDCK II), metabolic stability (plasma, microsomes and hepatocytes for a range of species), plasma protein binding (multiple species) and drug-drug interaction (DDI) potential (cytochrome P450, CYP, inhibition). Recent additions to our portfolio include human transporter assays (e.g. OATP1B1) and CYP induction analysis (PXR receptor, HepaRG cells or cryopreserved human hepatocytes). Additional bespoke studies are often accommodated to troubleshoot emerging challenges within projects.

Estimation of human pharmacokinetic parameters, dose and exposure provides a contemporary framework for multi-parameter optimisation.

Working with multiple partners across a variety of sectors provides Evotec with unique insight in several areas.



STAND-ALONE SCREENING

- Automated, high-throughput assays allows for profiling of several hundreds of compounds per week against a broad panel of DMPK assays
- Tailored packages designed to address a specific problem associated with a compound, or more frequently, a series of compounds

In the pharmaceutical industry, early assessment of liabilities of potential drug candidates is an important element to decrease the high attrition rate in the drug discovery and development process. One of the key challenges is optimising the balance between drug efficacy and potential adverse effects at the earliest possible point in time for de-risking cost-intensive activities especially during late-stage clinical development.

Once key liabilities are identified, DMPK assays can be applied to rapidly design out such properties, sometimes making use of quantitative structure-activity (QSAR) analysis. To meet this demand, Evotec has established an industrialised high-throughput profiling platform for routine compound screening against a panel of the most critical targets:

- Potential DDIs can be determined by using our panel of cytochrome P450 ("CYP") reversible inhibition ("RI") assays for the major CYP isoforms.
  - Assays for the four most highly relevant CYP isoforms are established on our high-throughput RapidFire/MS platform.
  - Medium-throughput LC/MS/MS based assays are provided for CYP1A2 and 2C19.
- For CYP3A4, analysis of time-dependent inhibition ("TDI") and induction are also provided.

In support of discovery chemistry programmes, externalisation of such activities is providing a unique business opportunity for some partners to reserve internal capacity for core research activities, expand their assay portfolio and to mitigate risk.

Pharmacological sensitivity and statistical robustness of the DMPK assays is routinely monitored by a range of reference compound DMPK assays are performed according to validated SOPs and provide 8-point IC50/EC50 for test compounds. Turnaround time from compound reception to data reporting is 7 working days. Assays are scaleable towards higher throughput.

Examples of capacity for our higher throughput assays

ASSAY	CAPACITY (WEEKLY)
Plasma protein binding (multiple species)	100
Permeability (e.g. MDCKII)	144
Microsomal stability (multiple species)	200
Hepatocyte stability (multiple species)	100
CYP inhibition (reversible)	200 – 800 (CYP-dependent)
CYP inhibition (time-dependent, CYP3A4 IC50 shift)	700
CYP Induction (hPXR)	800

TECHNOLOGY PLATFORM AND EXPERT KNOWLEDGE

Within many collaborations with major pharmaceutical and biotech companies, Evotec has successfully provided expert knowledge in development and integration of complex processes for our collaborator's drug discovery programmes including:

- Support logistics of compound shipments in close interaction with global carriers.
- Management of large libraries and regularly shipped smaller compound batches for DMPK or SAR profiling.
- Broad expertise in development and validation of >500 biochemical, biophysical and cell-based assays.
- Compound profiling using benchtop and fully automated screening platforms.
- State-of-the-art bioanalytical readout technologies including e.g. RapidFire/MS, FLIPR, SPR, fluorescence, radiometric, high-content imaging.
- Flexible data analysis to provide customised formats enabling rapid data uploads to internal or external data bases
- Professional project management with experienced leads

IN VIVO Pharmacokinetics & PKPD support

Obtaining pharmacokinetic data is a key requirement in the evaluation of new chemical entities providing validation of any *in vitro-in vivo* extrapolations and an understanding of ADME processes in pre-clinical species which can provide confidence in translation to Man and/or highlight key risks. As part of Evotec's integrated drug discovery platform, *in vivo* pharmacology studies are also further supported by DMPK and histology.

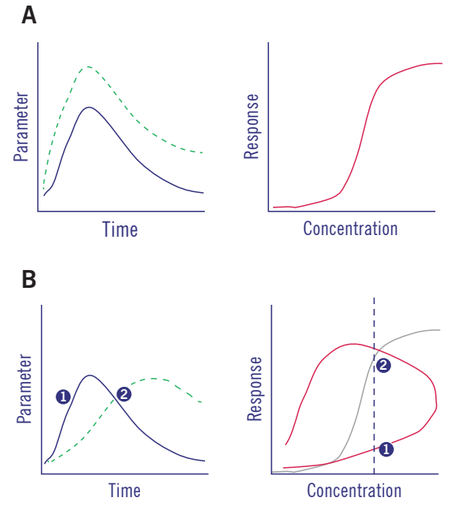
Evotec offers:

- Various administration routes: intravenous (incl. infusion), per os (PO), intraperitoneal, subcutaneous, intra-cerebrospinal and intramuscular.
- Cassette PK screening of up to 5 compounds simultaneously.
- Different sampling routes: jugular vein cannulation, cardiac puncture, tail vein microsampling, retro-orbital.
- Different matrices: blood, plasma, cerebrospinal fluid, tissues, bile, urine and faeces.
- Data generated with the latest version of Phoenix® WinNonlin®6.3 software, analysis performed using rigorous acceptance criteria.
- Solid state evaluation, salt screening and enhanced formulation for problematic compounds.
- Biomarker development and application within projects.

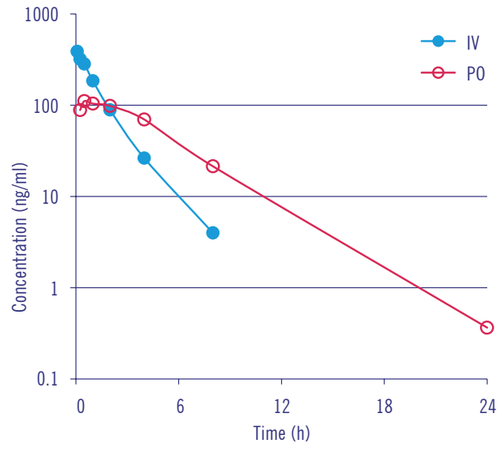
DMPK also provide analysis and interpretation of pharmacokinetic-pharmacodynamic (PKPD) relationships in support of PD and/or disease models conducted by our colleagues in Biology. It is important to emphasise here the need to study concentration–time and response–time profiles since the temporal relationship between these varies with different targets and the position of a target in a biological pathway. Hence the time to equilibrium between the plasma and target tissue can be very rapid (e.g. anti-thrombotic agent) or delayed (e.g. anti-psychotic).

Simulations from early PK data assist study design and relationships between response, concentration and time based on exposure (often in target tissues) support translation to Man and early assessments of clinical dose and associated exposure.

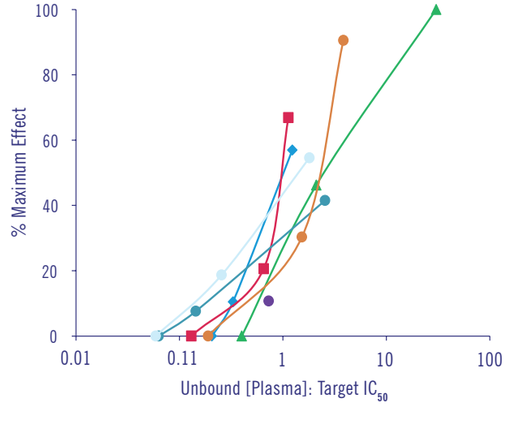
Analysis of biomarkers can greatly enhance this process. Integration of such information in static or ideally dynamic (physiologically-based pharmacodynamic; PBPK) models forms the foundation for DDI and safety risk assessment.



Schematic illustrating PKPD for rapid (A) and slower (B) equilibrating compounds



Representative PK profile from an oral bioavailability study



PK-PD plot for range of compounds illustrating value of considering unbound concentration in relation to affinity for the target